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EXAMINER
EPPERSON, JON D

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/661,927	DOWER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-77,138 and 139* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-77,138 and 139* is/are rejected.

7)☒ Claim(s) *64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/12/2006* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection (see 10/17/06 Response). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/13/07 has been entered. Claims 1 and 3-77 were pending. Applicants amended claim 1 and added claims 138 and 139. Therefore, claims 1, 3-77, 138 and 139 are currently pending and examined on the merits.

Please note that all previous restriction and/or species elections have been withdrawn with regard to the pending claims. In view of the above noted withdrawal of the restriction requirement as to the linked species, applicant(s) are advised that if any claim(s) depending from or including all the limitations of the allowable generic linking claim(s) be presented in a continuation or divisional application, such claims may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The Swanson et al. rejection under 35 U.S.C. § 102(b) is withdrawn in view of Applicants' amendments to claim 1.

New Rejections

Objections to the Claims

3. Claim 64 is objected to because of the following informalities:

A. Claim 64 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 64 depends on claim 1, which already contains different compounds derived from a combinatorial library.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1, 3-77, 138 and 139 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For independent ***claims 1, 69, 75-77 (and all dependent claims)*** use of the word "type" in the phrase "carrier-type" is vague and indefinite. The addition of the word

"type" to an otherwise definite expression extends the scope of the expression so as to render it indefinite. See *Ex parte Copenhaver*, 109 USPQ 118 (Bd. App. 1955). See also MPEP § 2173.05(b). The Examiner recommends "carrier-mediated transport protein" as a replacement. Therefore, claims 1, 69, 75-77 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

B. ***Claim 1*** recites the limitation "the plasma membrane of the cell surface" in line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 1 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. ***Claim 14*** recites the limitation "the plasma membrane of the cell surface" in line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 14 and all dependent claims are rejected under 35 USC 112, second paragraph.

D. ***Claim 56*** recites the limitation "the test compound" in line 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 56 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. ***Claims 4, 6, 12, 19, 20, and 22*** fail to particularly point out and distinctly claim the subject matter that the appellant regards as the invention because they depend on canceled claim 2. Therefore, claims 4,6, 12, 19, 20, 22 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

F. ***Claims 4, 12, 14, and 72*** recite the limitation "the carrier type protein." There is insufficient antecedent basis for this limitation in the claim. The previous claims only referred to "carrier type transport protein." Therefore, claim 4, 12, 14, 72 and all dependent claims are rejected under 35 USC 112, second paragraph.

G. ***Claims 6 and 70*** recite the limitation "the carrier type transporter protein." There is insufficient antecedent basis for this limitation in the claim. The previous claims only referred to "carrier type transport protein." Therefore, claim 6, 70 and all dependent claims are rejected under 35 USC 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 69 is rejected under 35 U.S.C. 102(b) as being anticipated by Homolya et al. (Homolya et al. "Fluorescent Cellular Indicators are Extruded by the Multidrug Resistance Protein" *J. Biol. Chem.* **1993**, *368(29)*, 21493-21496).

For ***claim 69***, Homolya et al. (see entire document) disclose a method for testing NIH-3T3 mouse fibroblasts stably expressing human multidrug transporter (MDR1) (e.g., see abstract), which reads on the claimed invention. For example, Homolya et al. disclose **(a)** providing one or more cells that express a carrier-type transport protein (e.g., see Homolya et al. abstract wherein NIH-3T3 cells are disclosed that express the MDR1 carrier-type transport protein). In addition, Homolya et al. disclose **(b)** contacting the one ore more cells with one or more complexes, each complex comprising a compound and a reporter (e.g., see figure 2 wherein the compound is AM and the reporter is Fura, Quin, Indo, Fluo, BCECF, calcein). Please note that although these compounds contain a fluorophore, they do not possess the requisite

compound/fluorophore/quencher structure and thus do not read on claim 1 and its dependent claims. In addition, Homolya et al. disclose **(c)** selectively detecting a signal from a reporter internalized within one or more of the cells as compared to signal from reporter outside the cell to indicate that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein (e.g., see abstract wherein the hydrophobic "AM" complexes are substrates but the AM derivatives cleaved by the cytoplasmic esterases are not.

6. Claims 69, 70, 72, 75, 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Swanson et al. (Swanson, S. J.; Bethke, P.; Jones, R. L. "Barley Aleurone Cells Contain Two Types of Vacuoles: Characterization of Lytic Organelles by Use of Fluorescent Probes" *The Plant Cell* **May 1998**, *10*, 685-698) (of record) as evidenced by Ozkan et al. (Ozkan P.; Mutharasan, R. "A rapid method for measuring intracellular pH using BCECF-AM" *Biochim. Biophys. Acta.* **2002**, *1572*, 143-148) (of record).

For ***claims 69***, Swanson et al. (see entire document) disclose the use of a library of fluorescent conjugates in screening and/or characterizing two forms of vacuoles, protein storage vacuoles and secondary vacuoles, in protoplasts of barley aleurone (e.g., see Swanson et al., abstract; see also Table 1), which anticipates the claimed invention. For example, Swanson et al. disclose **(a)** providing one or more cells, each cell expressing a carrier-type transport protein such as a population of living barley aleurone cells expressing organic anion and glutathione conjugate transporters (e.g., see abstract wherein cells are disclosed; see also page 686, column 1, last paragraph; see also page 695, column 1, paragraph 2, "we conclude that at least two kinds of ATP-dependent

transporters are present in protein storage vacuoles. One of these is an organic anion transporter that can be inhibited by probenecid and transports BCECF. The other is a glutathione conjugate transporter that is not inhibited by probenecid and transports MCB-GS. Both transporters may belong to the superfamily of ABC transporters"). Swanson et al. also disclose **(b)** contacting the one or more cells with one or more complexes each complex comprising a compound and a reporter (e.g., see Table 1). For example, Swanson et al. disclose the use of BCECF-AM, ZFR-GMAC, and ZFR-CMAC-GS (e.g., see Table 1, see also figure 4; see also pages 687-688) wherein the different compound represents the "AM" or "ZFR" portions and the reporter represents the cleaved "BCECF" or the "CMAC-GS" (e.g., see figure 4; see also Table 1; see also figure 3; see also discussion; see also Ozkan et al., poage 143, column 2, paragraph 1, disclosing cleavage mechanism for BCECF-AM, "... intracellular esterases cleave the ester bond releacing BCECF, which fluoresces according to the intrcellular pH"). Finally, Swanson et al. discloses **(c)** detecting a signal from a reporter internalized within the one or more of the cells as compared to signal from reporter outside the cell to indicate that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport. (e.g., see figures showing uptake of various conjugates; see especially figure 4 showing preferential generation of signal for proteolytically cleaved ZFR-CMAC-GS; see also discussion with regard to ZFR-GMAC-GS and conclusion identifying this compound as a substrate for a glutathione conjugate transporter that is a member of the ABC superfamily e.g., see page 695, column 1, paragraph 1).

For ***claim 70***, Swanson et al. disclose the method of claim 69 wherein the erporter

comprises a fluorophore and a quencher moiety, and if a compound complexes with the reporter is a substrate for the carrier-type transporter protein, the complex is transported by the carrier-type transport protein into a cell expressing the carrier-type transport protein, whereby the quencher moiety becomes separated from the fluorophore such that a fluorescent signal is emitted by the fluorpohpore within the cell, and the detection step comprises detecting the fluorescent signal (e.g., see figure 4 showing preferential cleavage of ZFR-GMAC-GS to GMAC-GS wherein a signal is preferentially generated upon internalization; see also Ozkan et al., page 143, column 2, paragraph showing that BCECF-AM is cleaved to BCECF for signal generation upon internalization of BCECF-AM into the cell; see also figures in Swanson et al. showing results of conjugate uptake).

For ***claim 72***, Swanson et al. disclose the enzymatic cleavage of ZFR-CMAC-GS to GMAC-GS substrates (e.g., see figure 4; see also page 688, column 1, last paragraph; see also Ozkan et al., page 143, column 2, paragraph 1).

For ***claim 75***, Swanson et al. disclose a method of screening for a carrier type transport protein and/or a ligand thereto comprising **(a)** providing a plurality of different cells that are located within a single reaction vessel each cell expressing a carrier type transport protein and different cells having different distinguishable characteristics For example, Swanson et al. disclose both protein storage and lysosome-like secondary vacuoles, which can be considered a population of cells or, alternatively, the population of cells is differentiated by the addition of (e.g., see figures 1 and 4 showing hormone treatments) or, alternatively, the cells are different based on the addition of various inhibitors and compared to as compared to a control cell wherein the identity of various

cells is determined by microscopy (e.g., see figure 9), see also figure 1 showing differentiation of morphology of protein storage vacuoles versus secondary vacuoles; see also page 686, column 2, last paragraph). Swanson et al. further disclose **(b)** contacting the plurality of different cells with one or more complexes each complex comprising a compound and a reporter whereby at least one complex is bound to or internalized within one of the cells (e.g., see Table 1). For example, Swanson et al. disclose the use of BCECF-AM, ZFR-GMAC, and ZFR-CMAC-GS (e.g., see Table 1; see also figure 4; see also pages 687-688) wherein the different compound represents the "AM" or "ZFR" portions and the reporter represents the cleaved "BCECF" or the "CMAC-GS" (e.g., see figure 4; see also Table 1; see also figure 3; see also discussion; see also Ozkan et al., poage 143, column 2, paragraph 1, disclosing cleavage mechanism for BCECF-AM, "... intracellular esterases cleave the ester bond releacing BCECF, which fluoresces according to the intrcellular pH"). Swanson et al. also disclose **(c)** detecting a signal from the reporter of the at least one complex bound to or internalized within the cell in step (b) (e.g., see figures showing uptake of various conjugates; see especially figure 4 showing preferential generation of signal for proteolytically cleaved ZFR-CMAC-GS; see also discussion with regard to ZFR-GMAC-GS and conclusion identifying this compound as a substrate for a glutathione conjugate transporter that is a member of the ABC superfamily e.g., see page 695, column 1, paragraph 1). Finally, Swanson et al. disclose **(d)** determining the identity of the cell in step (b) from its distinguishable characteristic (e.g., see page 695, column 1, paragraph 2, "we conclude that at least two kinds of ATP-dependent transporters are present in protein storage vacuoles. One of these

is an organic anion transporter that can be inhibited by probenecid and transports BCECF. The other is a glutathione conjugate transporter that is not inhibited by probenecid and transports MCB-GS. Both transporters may belong to the superfamily of ABC transporters").

For ***claim 76***, Swanson et al. disclose a method of screening for a carrier type transport protein and/or a ligand thereto comprising **(a)** providing one or more cells each cell expressing a carrier type transport protein and located in a single reaction vessel (e.g., see abstract wherein cells are disclosed; see also page 686, column 1, last paragraph; see also page 695, column 1, paragraph 2, "we conclude that at least two kinds of ATP-dependent transporters are present in protein storage vacuoles. One of these is an organic anion transporter that can be inhibited by probenecid and transports BCECF. The other is a glutathione conjugate transporter that is not inhibited by probenecid and transports MCB-GS. Both transporters may belong to the superfamily of ABC transporters"). Swanson et al. also disclose **(b)** contacting the one or more cells with a plurality of different complexes each complex comprising a compound and a reporter the compound and reporter varying between different complexes and different reporters disposed to generate different signals whereby at least one complex is bound to or internalized within the one or more cells (e.g., see Table 1). For example, Swanson et al. disclose the use of BCECF-AM, ZFR-GMAC, and ZFR-CMAC-GS (e.g., see Table 1, see also figure 4; see also pages 687-688) wherein the different compound represents the "AM" or "ZFR" portions and the reporter represents the cleaved "BCECF" or the "CMAC-GS" (e.g., see figure 4; see also Table 1; see also figure 3; see also discussion;

see also Ozkan et al., page 143, column 2, paragraph 1, disclosing cleavage mechanism for BCECF-AM, "... intracellular esterases cleave the ester bond releasing BCECF, which fluoresces according to the intrcellular pH"). Finally, Swanson et al. disclose **(c)** detecting the signal from the reporter of the at least one complex the signal providing an indication of the identity of the compound borne by the at least one complex (e.g., see figures showing uptake of various conjugates; see especially figure 4 showing preferential generation of signal for proteolytically cleaved ZFR-CMAC-GS; see also discussion with regard to ZFR-GMAC-GS and conclusion identifying this compound as a substrate for a glutathione conjugate transporter that is a member of the ABC superfamily e.g., see page 695, column 1, paragraph 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 14, 2007

JON EPPERSON
PRIMARY EXAMINER